

# ANZCOR Guideline 14.2 – Acute Coronary Syndromes: Initial Medical Therapy

## Guideline

### Who does this guideline apply to?

This guideline applies to adult victims.

### Who is the audience for this guideline?

This guideline is for use by health professionals.

## 1 Symptomatic Therapy

There are a number of therapies in patients with Acute Coronary Syndromes (ACS) that provide relief for symptoms.

Supplemental oxygen should be initiated only if the patient has breathlessness, hypoxaemia ( $SpO_2 < 94\%$ ), or signs of heart failure or shock. The use of oxygen saturation monitoring by non-invasive techniques such as pulse oximetry, may be very useful in guiding oxygen therapy<sup>2</sup> (weak recommendation, very-low-quality evidence)<sup>3</sup>. However, it is important to understand that there is evidence that hyperoxaemia is potentially harmful in uncomplicated myocardial infarction<sup>3,4</sup>. (LOE IV). Oxygen may have a separate indication in other emergency situations at times associated with ACS however (e.g. water accidents, gas embolism etc.).

Morphine analgesia is also important symptomatic relief for patients with chest pain. Morphine may be considered for patients with ongoing symptoms of chest discomfort<sup>5</sup> and titrated to relieve pain. (LOE IV). Value is placed on relieving pain and distress understanding that the evidence of benefit is lacking and further research is required regarding the possibility of harm suggested in some registry data<sup>5</sup>.

While anxiolytics may be administered to relieve anxiety in patients with ACS but there is no evidence that it improves outcomes for patients in terms of ECG resolution, reduced infarct, decreased mortality or morbidity in patients with suspected ACS<sup>6</sup>. (LOE IV)

Nitroglycerine administration may be of benefit within 3 hours of the onset of symptoms in patients with infarction in the era prior to the advent of reperfusion therapy (based on extrapolation from other contexts)<sup>7-9</sup>. In the current era no trial has specifically evaluated patients in the Emergency Department (ED) or prehospital settings. It is reasonable to consider the early administration of nitroglycerin in selected patients without contraindications, particularly if this provides pain relief.

There is however a lack of evidence to support or refute the routine administration of nitroglycerin in the ED or prehospital setting in patients with a suspected ACS. (LOE IV)  
Specifically in cocaine-associated chest pain lorazepam and nitroglycerine may be useful in the alleviation of chest pain in this specific setting.

In general non-steroidal anti-inflammatory drugs (NSAIDs) should not be administered in patients with suspected ACS as they could be harmful<sup>10</sup>. Further, patients with suspected ACS who are taking NSAIDs should have these discontinued if it is feasible. (LOE I).

## **2 Antiplatelet and Anticoagulant Therapy**

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### **2.1 Aspirin administration**

The early administration of aspirin in an antiplatelet dose of 300 mg is recommended in patients with suspected ACS where contraindications such as true anaphylaxis or bleeding disorder have been excluded<sup>11</sup>. The patients should be directed to chew the tablet (which should not be enteric coated). Dissolvable aspirin is preferred<sup>12-15</sup>.

There is currently limited evidence to directly support the strategy of dispatcher directed or bystander administration of aspirin, however, it is considered to be a reasonable approach if the carer is able to exclude a history of true anaphylaxis or bleeding disorder<sup>15-18</sup>. (LOE IV).

### **2.2 Antiplatelet Agents**

**Clopidogrel:** Clopidogrel is a thienopyridine that inhibits P2Y<sub>12</sub> platelet receptor. The drug requires activation by a two stage biotransformation within the liver. This is a process that is modulated by genetic polymorphisms resulting in variability in clinical effect<sup>19</sup>. Benefit has been demonstrated when added to aspirin in non-ST elevation acute coronary syndrome (NSTEMACS) patients, including those treated with percutaneous coronary intervention (PCI). Reductions in cardiovascular death, myocardial infarction (MI) and stroke have been observed but with an increase in major bleeding<sup>20</sup>. It is recommended that patients who have moderate to high risk NSTEMACS and ST-elevation myocardial infarction (STEMI) receive clopidogrel in addition to the standard care (aspirin, anticoagulation and/or a reperfusion). The ideal dose in older patients has not yet been determined. However, in patients under the age of 75 years the loading dose of clopidogrel is 600 mg if PCI is planned or 300 mg if a non-invasive strategy with fibrinolysis is the planned treatment option<sup>21,22</sup>. (LOE II).

**Prasugrel:** Prasugrel is a new thienopyridine, that produces more rapid and consistent platelet inhibition<sup>19</sup>. In the clopidogrel naïve patient, prasugrel (compared to clopidogrel) reduced the incidence of myocardial infarction in patients with moderate to high risk NSTEMACS and patients with STEMI planned for primary PCI. Prasugrel has been associated with a higher rate of bleeding complications in patients >75 years of age, those with a history of stroke or transient ischaemic attack and body weight less than 60 kg. Prasugrel is not recommended in patients with STEMI who have received fibrinolysis. It may be used in place of clopidogrel in patients with STEMI of less than 12 hours duration where PPCI is planned<sup>23</sup>. (LOE II)

In patients with NSTEMI, prasugrel may be administered after angiography when the coronary anatomy is known and the plan is to proceed to PCI.

Prasugrel may be administered as a loading dose of 60 mg in place of clopidogrel in these patients with ACS as long as they are not at high risk from bleeding. (LOE II).

**Ticagrelor** is a pyrimidine derivative, which binds reversibly to the P2Y<sub>12</sub> receptor without the need for biotransformation. Like prasugrel, it has a more rapid and consistent onset of action compared with clopidogrel, but additionally it has a quicker offset of action so that recovery of platelet function is faster<sup>19</sup>.

Ticagrelor has demonstrated some benefits over clopidogrel in patients with moderate to high risk NSTEMACS (treated conservatively or invasively) and patients with STEMI planned for primary PCI (PPCI) in terms of a reduction in death from vascular causes and MI. There was no increase in major bleeding observed but an increase in minor bleeding was seen<sup>24</sup>.

The adverse effects of ticagrelor include dyspnoea, increased frequency of mostly asymptomatic ventricular pauses, and asymptomatic increases in uric acid.

Ticagrelor is recommended for patients at moderate-to-high risk of ischaemic events (e.g. troponin positive ACS), regardless of initial planned treatment strategy and including those pre-treated with clopidogrel. The dose is 180-mg loading dose and then 90 mg twice daily. (LOEII). Ticagrelor may be used then in place of clopidogrel in patients with ACS.

The risks and benefits of combinations of the newer antiplatelet agents are undetermined. It is expected that whilst patients may be switched from one agent to another, the drugs should not be used in combination with each other on an ongoing basis. They are expected to be used in combination with aspirin on an ongoing basis.

Prehospital administration of these agents in the setting of STEMI in recent studies has shown no mortality benefit or harm in the administration of either ticagrelor or clopidogrel<sup>(ref 14.2 NA)</sup>. ANZCOR suggest that when ADP-receptor antagonists are given to suspected STEMI patients with a planned primary PCI approach, administration can occur in either the prehospital or in-hospital setting, but there is insufficient evidence to change existing practice (CoSTR 2015, very-low-quality evidence, weak recommendation)<sup>3</sup>. The pre hospital administration of ticagrelor when compared with placebo, showed evidence of reduced subacute stent thrombosis.<sup>25</sup> Typically the delays between first medical contact and PPCI are relatively short and the administration of these agents can occur either prehospital or in-hospital. It is important that the initial management of STEMI including the prehospital use of these agents is undertaken within an appropriate model of care with close communication between physicians, PCI facility cardiologists and emergency staff. This will also need to take into account geographic, population and resource factors and local systems of care.

## 3 Anticoagulants

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### 3.1 Anticoagulants in NSTEMACS

In patients presenting with NSTEMACS, anticoagulation with enoxaparin or unfractionated heparin (UFH) is a reasonable treatment strategy<sup>26</sup>. (LOE I) This recommendation includes patients managed with an initial conservative approach or a planned invasive approach.

Recent studies have suggested that bivalirudin is an alternative anticoagulant to heparin. It is considered an effective alternative<sup>27-30</sup>. (LOE II). There is however, no definite evidence that it offers an advantage over UFH or enoxaparin where these agents are used without a glycoprotein IIB/IIIA inhibitor. When heparin is used routinely combined with a glycoprotein IIB/IIIA inhibitor, composite ischaemic end points are similar but bleeding is increased compared to bivalirudin and the provisional use of a glycoprotein IIB/IIIA inhibitor.

In patients with renal impairment, those at increased bleeding risk but where anticoagulation therapy is not contraindicated, it may be a reasonable option to treat with bivalirudin. UFH may also be considered while, enoxaparin may be best avoided with renal impairment. There is no specific evidence for or against anticoagulant use in non-ST elevation ACS in the pre-hospital setting. (LOE II).

### **3.2 Anticoagulants in STEMI treated with Fibrinolysis**

In patients with STEMI in the pre-hospital and ED setting, the issue of anticoagulant choice needs to be considered. In patients with STEMI managed with fibrinolysis, anticoagulation with either enoxaparin or UFH is reasonable<sup>31-35</sup>. (LOE I).

However, in all situations these agents should not be switched from enoxaparin to UFH or vice versa as this has been shown to be associated with an increased bleeding risk. (Class B;LOE II).

### **3.3 Anticoagulants in STEMI treated with PCI**

In patients with suspected STEMI in the pre-hospital and ED setting there are a number of anticoagulants available to treat patients including bivalirudin and enoxaparin. Enoxaparin may be considered a safe and effective alternate to UFH in the patient with STEMI undergoing contemporary PCI<sup>3</sup> (CoSTR 2015, weak recommendation, low-quality evidence). However, to avoid increased bleeding risks, patients initially treated with enoxaparin or UFH should not be switched<sup>36-38</sup>. (LOE II). The administration of anticoagulant in patients with suspected STEMI and a planned PPCI can occur in-hospital or in the pre-hospital setting (CoSTR 2015, weak recommendation, very-low-quality evidence)<sup>3</sup>.

Bivalirudin may be superior to UFH plus glycoprotein IIB/IIIA inhibitors with respect to bleeding complications and reduces adverse cardiac events and mortality in STEMI patients undergoing primary PCI<sup>39</sup>. There is however, increased rate of stent thrombosis observed in patients treated with bivalirudin in the first 24 hours<sup>40-44</sup>. There is insufficient data to speculate on the use of bivalirudin versus UFH or enoxaparin alone in patients undergoing PCI. We do not recommend change to existing practice of using UFH or enoxaparin. (CoSTR weak recommendation, very-low-quality evidence)<sup>3</sup>. (LOE II).

### **3.4 Glycoprotein IIB/IIIA inhibitors**

There have been recent studies that have called into question the value of the routine use of glycoprotein IIB/IIIA inhibitor use in patients with suspected STEMI or non-STEMI in the pre-hospital and ED setting<sup>45</sup>. There may still be a role for glycoprotein IIB/IIIA inhibitors in selected high risk patients with NSTEMI-ACS in whom a PCI is planned. There are increased bleeding risks with the routine use of these agents. (LOE II).

### 3.5 Fondaparinux

Fondaparinux has no indication for ACS in Australia and New Zealand.

## 4 Optimal Medical Therapy for Primary and Secondary Prevention

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There are a number of additional medical therapies that have been proposed for ACS patients to reduce myocardial ischaemia and recurrent major cardiovascular events, and improve long-term survival. Therapeutic options in the pre-hospital and emergency setting that should be specifically addressed include the routine use of antiarrhythmics, beta blockers, angiotensin converting enzyme (ACE) inhibitors and HMG CoA-reductase inhibitors.

### 4.1 Antiarrhythmics

There is little evidence to suggest that the prophylactic use of antiarrhythmics improves outcomes in patients with ACS<sup>46-49</sup>. The prophylactic use of antiarrhythmic agents is not recommended. (LOE II).

### 4.2 Beta Blockers

Routine use of IV beta blockers in the pre-hospital setting or during initial assessment in the ED is not supported by the available evidence<sup>50-52</sup>. It may be useful to administer IV beta blockers in specific settings such as severe hypertension or tachycardia when no contraindication exists. (LOE I).

### 4.3 ACE Inhibitors

ACE inhibitors and angiotensin receptor blocker agents reduce mortality in patients with acute myocardial infarction<sup>53,54</sup>. However there is insufficient evidence to support the routine initiation of these in the pre-hospital or ED setting. (LOE IV)

### 4.4 Lipid Lowering Therapy

Statins should be considered early after the onset of ACS. In patients presenting with ACS, unless it is contraindicated, pre-existing statin therapy should be continued<sup>55-57</sup>. There are no reports on the risk or safety of an early administration of statins. Most studies document treatment within the first 24 hours after presentation. (LOE IV)

### 4.5 Calcium channel blockers

There is little data to support the routine use of calcium channel blockers in the pre hospital and emergency setting. Reductions in mortality have not been reported in this setting<sup>58</sup>.

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